

Amendments to the Claims

Please cancel claims 1-50, without prejudice or disclaimer. Please add new claims 51-81 as follows:

1-50. (Cancelled)

51. (New) An isolated human monoclonal antibody comprising a human heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a human light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein:

(a) the human heavy chain variable region CDR3 sequence is selected from the group consisting of amino acid residues 99-113 of SEQ ID NO: 2, amino acid residues 99-111 of SEQ ID NO: 6, amino acid residues 99-111 of SEQ ID NO: 10, and conservative modifications thereof;

(b) the human light chain variable region CDR3 sequence is selected from the group consisting of amino acid residues 89-97 of SEQ ID NO: 4, amino acid residues 89-97 of SEQ ID NO: 8, amino acid residues 89-98 of SEQ ID NO: 12, and conservative modifications thereof;

(c) the human antibody binds to HER2/neu with an affinity constant ( $K_A$ ) of at least  $10^7 \text{ M}^{-1}$ ; and

(d) the human antibody inhibits growth of a tumor cell expressing HER2/neu.

52. (New) The human antibody of claim 51, wherein the human heavy chain variable region CDR2 sequence is selected from the group consisting of amino acid residues 50-66 of SEQ ID NO: 2, amino acid residues 50-66 of SEQ ID NO: 6, amino acid residues 50-66 of SEQ ID NO: 10, and conservative modifications thereof; and the human light chain variable region CDR2 sequence is selected from the group consisting of amino acid residues 50-56 of SEQ ID NO: 4, amino acid residues 50-56 of SEQ ID NO: 8, amino acid residues 50-56 of SEQ ID NO: 12, and conservative modifications thereof.

53. (New) The human antibody of claim 51, wherein the human heavy chain variable region CDR1 sequence is selected from the group consisting of amino acid residues 31-35 of SEQ ID NO: 2, amino acid residues 31-35 of SEQ ID NO: 6, amino acid residues 31-35 of SEQ ID NO: 10, and conservative modifications thereof; and the human light chain variable region CDR1 sequence is selected from the group consisting of amino acid residues 24-34 of SEQ ID NO: 4, amino acid residues 24-34 of SEQ ID NO: 8, amino acid residues 24-34 of SEQ ID NO: 12, and conservative modifications thereof.

54. (New) The human antibody of claim 51, wherein the antibody is produced from a transgenic non-human animal.

55. (New) The human antibody of claim 51, wherein the antibody mediates cytotoxicity of the tumor cell expressing HER2/neu in the presence of human effector cells.

56. (New) The human antibody of claim 51, wherein the antibody binds to human HER2/neu with an affinity constant ( $K_A$ ) of at least  $10^8 \text{ M}^{-1}$ .

57. (New) The human antibody of claim 51, wherein the antibody binds to human HER2/neu with an affinity constant ( $K_A$ ) of at least  $10^9 \text{ M}^{-1}$ .

58. (New) The human antibody of claim 51, wherein the antibody dissociates from human HER2/neu with a rate constant ( $K_{\text{dis}}$ ) of about  $10^{-3} \text{ S}^{-1}$  or less.

59. (New) The human antibody of claim 51, wherein the tumor cell is selected from the group consisting of an adenocarcinoma cell, a salivary gland carcinoma cell, a stomach cancer cell, a kidney cancer cell, a mammary gland carcinoma cell, a lung carcinoma cell, a squamous cell carcinoma cell, and an ovarian cancer cell.

60. (New) The human antibody of claim 51, wherein the antibody inhibits tumor cell growth by at least about 60%.

61. (New) The human antibody of claim 51, wherein the antibody does not bind to EGFR.

62. (New) The human antibody of claim 51, wherein the antibody heavy chain is an IgG1 or IgG3 heavy chain.

63. (New) The human antibody of claim 51, which is an antibody fragment or a single chain antibody.

64. (New) An isolated human monoclonal antibody comprising a human heavy chain variable region and a human light chain variable region, wherein:

(a) the human heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 6, 10, and sequences that are at least 80% homologous to SEQ ID NOs: 2, 6, and 10;

(b) the human light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 8, and 12, and sequences that are at least 80% homologous to SEQ ID NOs: 4, 8, and 12;

(c) the human antibody binds to HER2/neu with an affinity constant ( $K_A$ ) of at least  $10^7 \text{ M}^{-1}$ ; and

(d) the human antibody inhibits growth of a tumor cell expressing HER2/neu.

65. (New) An isolated human monoclonal antibody comprising human heavy chain and human light chain variable regions comprising the amino acid sequences shown in SEQ ID NO:2 and SEQ ID NO:4, respectively.

66. (New) An isolated human monoclonal antibody comprising human heavy chain and human light chain variable regions comprising the amino acid sequences shown in SEQ ID NO:6 and SEQ ID NO:8, respectively.

67. (New) An isolated human monoclonal antibody comprising human heavy chain and human light chain variable regions comprising the amino acid sequences shown in SEQ ID NO:10 and SEQ ID NO:12, respectively.

68. (New) An isolated human monoclonal antibody comprising:  
(a) a heavy chain variable region having CDR1, CDR2 and CDR3 sequences set forth as amino acids 31-35, amino acids 50-66 and amino acids 99-113 of SEQ ID NO: 2, respectively; and  
(b) a light chain variable region having CDR1, CDR2 and CDR3 sequences set forth as amino acids 24-34, amino acids 50-66 and 89-97 of SEQ ID NO: 4, respectively,  
wherein the antibody binds HER2/Neu.

69. (New) An isolated human monoclonal antibody comprising:  
(a) a heavy chain variable region having CDR1, CDR2 and CDR3 sequences set forth as amino acids 31-35, amino acids 50-66 and amino acids 99-111 of SEQ ID NO: 6, respectively; and  
(b) a light chain variable region having CDR1, CDR2 and CDR3 sequences set forth as amino acids 24-34, amino acids 50-66 and 89-97 of SEQ ID NO: 8, respectively,  
wherein the antibody binds HER2/Neu.

70. (New) An isolated human monoclonal antibody comprising:  
(a) a heavy chain variable region having CDR1, CDR2 and CDR3 sequences set forth as amino acids 31-35, amino acids 50-66 and amino acids 99-111 of SEQ ID NO: 10, respectively; and  
(b) a light chain variable region having CDR1, CDR2 and CDR3 sequences set forth as amino acids 24-34, amino acids 50-66 and 89-98 of SEQ ID NO: 12, respectively,  
wherein the antibody binds HER2/Neu.

71. (New) An isolated human monoclonal antibody comprising:
- (a) a heavy chain variable region of a human V<sub>H</sub> 3-33 gene; and
  - (b) a light chain variable region of a human V<sub>K</sub> L6 gene,
- wherein the antibody binds HER2/Neu.
72. (New) An isolated human monoclonal antibody comprising:
- (a) a heavy chain variable region of a human V<sub>H</sub> 3-23 gene; and
  - (b) a light chain variable region of a human V<sub>K</sub> L15 gene,
- wherein the antibody binds HER2/Neu.
73. (New) An isolated human monoclonal antibody comprising:
- (a) a heavy chain variable region of a human V<sub>H</sub> 3-33 gene; and
  - (b) a light chain variable region of a human V<sub>K</sub> L15 gene,
- wherein the antibody binds HER2/Neu.
74. (New) A composition comprising the human antibody of claim 51 and a pharmaceutically acceptable carrier.
75. (New) An immunoconjugate comprising the human antibody of claim 51 linked to a therapeutic agent.
76. (New) The immunoconjugate of claim 75 wherein the therapeutic agent is a cytotoxin.
77. (New) A composition comprising the immunoconjugate of claim 76 and a pharmaceutically acceptable carrier.
78. (New) A bispecific molecule comprising the human antibody of claim 51 and a second binding specificity for an Fc receptor.

79. (New) The bispecific molecule of claim 78, wherein the Fc receptor is a human Fc $\gamma$  receptor or a human Fc $\alpha$  receptor.

80. (New) A method of inhibiting growth of a tumor cell expressing HER2/neu, comprising contacting the tumor cell with a human antibody according to claim 51, such that the growth of the tumor cell is inhibited.

81. (New) The method of claim 80, wherein the tumor cell is selected from the group consisting of an adenocarcinoma cell, a salivary gland carcinoma cell, a stomach cancer cell, a kidney cancer cell, a mammary gland carcinoma cell, a lung carcinoma cell, a squamous cell carcinoma cell, and an ovarian cancer cell.